International Journal of Gynecological Cancer

Borderline ovarian tumours: Fifteen years' experience at a Scottish tertiary cancer centre

--Manuscript Draft--

Manuscript Number:	IGC-D-18-00373R1
Full Title:	Borderline ovarian tumours: Fifteen years' experience at a Scottish tertiary cancer centre
Short Title:	Borderline Ovarian Tumours
Article Type:	Original Study
Manuscript Classifications:	Ovarian Cancer; Surgery
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Manuscript Region of Origin:	UNITED KINGDOM
Abstract:	Objectives Since the recognition of borderline ovarian tumours (BOT) in the 1970's the management of this subset of epithelial ovarian tumours has presented a challenge to clinicians. The majority present at an early stage but diagnosis is often only made following surgery, hence the heterogeneity of surgical management. BOT are morphologically diverse, and their behaviour is subsequently also heterogeneous. We aimed to assess recurrence rates and the rate of malignant transformation in patients diagnosed with BOT. Secondary objectives included a review current management and assessment of tumour markers, stage, cyst dimensions and the presence of micro-papillary features as prognostic indicators of recurrence. Methods/materials This retrospective cohort study included all patients treated with BOT between 2000 and 2015 in the South-east region of Scotland. Clinical, surgicopathological and follow-up data were collated. Data were analysed with reference to recurrence and malignant transformation. Results 275 patients underwent treatment for BOT in the study period. Surgical management was highly variable. A diagnosis of recurrent/persistent BOT or ovarian malignancy following initial treatment of BOT was rare with only 12/275 (4%) cases. There were 7 (3%) cases of ovarian malignancy. Advanced FIGO stage was the most prominent prognostic factor. Elevated pre-operative serum CA125 and the presence of micro-papillary features correlated with advanced stage at presentation. With a lack of clear guidance, follow up was highly variable with a median of 43 months (0 - 136). Conclusions To our knowledge this study is the largest BOT cohort in the UK. Recurrent disease is rare in optimally staged, completely resected, early stage BOT, without high risk features. Caution is needed in women electing not to undergo completion staging after

	diagnosis and in those opting for a fertility-preserving approach. Thorough informed consent and clear plans for surveillance and follow-up are needed with consideration of delayed completion surgery as appropriate.
Response to Reviewers:	We thank the reviewer for their comments regarding our manuscript 'Borderline ovarian tumours: Fifteen years' experience at a Scottish tertiary cancer centre'. We have considered the comments and have amended the manuscript accordingly. In response to the questions posed by the reviewer: The results show a very high rate of laparotomy compared to laparoscopy: 90% versus 10%. How do the authors explain this rate? 1.We agree that the laparotomy rate in this series was higher (90%) than reported by other groups. The proportion of patients undergoing laparoscopy increased over the 15- year period, rising from 3% in the first 5 years to 16% in the final 5 years reflecting a growing acceptance of the safety of this approach between 2000 - 2015. The high rate of laparotomy may also be a reflection of the relatively high median diameter of tumours (16.5 cm) in this cohort compared to those reported in the literature examining laparoscopic management of BOT (7.5 cm) and concern regarding rupture and extraction of such large volume tumours 1. Previous series examining cyst diameter have suggested that laparoscopic management might be restricted to low volume cysts 2. We have added explanation of this to the discussion in lines 206-215. What was the value of CA 19.9 in case of mucinous tumors? 2.Historically, CA 19.9 has not been used in the investigation of ovarian masses, mucinous or other histological subtypes in Scotland and this is reflected in our national guidelines (SIGN 135/ NICE). We agree with the reviewer and acknowledge that CA19.9 levels are commonly elevated in the presence of mucinous ovarian tumours and can be useful in the diagnosis of peritoneal carcinomatosis originating from the gastrointestinal tract. Nevertheless, given that markedly elevated CA19.9 levels can be found in benign mucinous disease 3, the routine use of CA19.9 to predict histological subtype of ovarian mucinous tumours is not currently supported within the NHS in Scotland. As such we regret that this data is not available for the patients within this retrospective cohort. Why no frozen section has be done? 3.Resources within our regional public health system did not allow the regular provision of resources for intraoperative frozen section (discussed in line 195 in the submitted draft) in all hospitals included in the study throughout the study period and as such management of BOT developed in the absence of this resource. Furthermore, historically there were concerns regarding the reliability and accuracy of frozen section diagnosis of BOT. With accumulating evidence and the provision of further resources this is now regularly employed in our centre. Additionally, the role of frozen section for the intra-operative diagnosis of borderline tumour must be carefully considered as it is unlikely to affect the surgical procedure undertaken in the group of patients who do not wish for a fertility sparing approach. In the setting of an isolated ovarian mass a frozen section result of BOT would not justify routine lymph node dissection in addition to a planned hysterectomy, BSO and omental biopsy. The histological subtyping of tumours using frozen section is not always possible and the benefit of appendicectomy for a macroscopically normal appendix in the setting of a mucinous BOT remains unclear. We believe that frozen section is not adequately precise to dictate intra-operative decision making regarding fertility decisions and it would be preferred in this subgroup of patients to undertake a second procedure as necessary following full histology reporting and opportunity for counselling. We have modified the discussion accordingly, lines 195-205. A table should be done to resume patients and tumours characteristics and surgery procedure 4.We have included a table summarising the descriptive data of the patient cohort, tumour characteristics and surgery undertaken. The mean follow -up is short: 43 months explaining the low rate of recurrence (<4%). 5.We acknowledge the overall short length of formal follow-up of the cohort, with a median of 43 months. This is skewed by the patients discharged to their general practitioners without any hospital based follow-up and those who were discharged prior to the traditional 5 years of follow-up, described in line 171. This variable practice is perhaps a reflection of the lack of national guidance regarding recommended follow up

and of the movement towards patient-initiated follow up in the UK. In our health service patients remain under the care of their general practitioner following discharge and with a relatively established population with low rates of relocation we depend upon re-referral to the treating centre if there is suspicion of recurrence.

Ovarian function was preserved only in 58 patients while 130 patients were pre-menopausal. It represents a very low rate of conservative surgery.
6.We agree with the reviewer that this cohort demonstrates a relatively low rate of conservative surgery (45%), although we note that this is higher than the large series reported by the AGO group (28%) 4. We suggest that the 15-year period over which time this study was conducted has coincided with a shift towards more conservative treatment for BOT as evidence of the safety of this approach has accumulated and patient management earlier in the cohort may reflect a more radical approach to treatment. The decision to proceed with radical surgery is made by the patient following careful counselling and with fully informed consent. Ovarian preservation is routinely presented as an option in pre-menopausal patients when appropriate and these figures represent the healthcare choices of our population in real practice.

Why one patient received adjuvant chemotherapy for FIGO stage 3c SBOT while invasive implants were excluded?
7.The decision-making process behind the administration of adjuvant chemotherapy to a single patient with FIGO stage 3C SBOT is not clear. This demonstrates the limitations created by the retrospective nature of this study. No invasive implants were identified, and the patient underwent complete surgical staging with no residual disease. This was undertaken in 2008 and review of the patient's records does not provide further elucidation. We include the report of this patient for completeness of the dataset.
In the conclusion the authors recommend to perform lymph node assessment in non-mucinous borderline ovarian tumours while this has been disused and that this is not free of morbidity.
8.We agree with the reviewer that there is no value in lymph node sampling or complete dissection in BOT and this should therefore not be performed routinely. Current UK guidelines, however suggest removal of bulky nodes and in keeping with this we would encourage examination/palpation of lymph node chains to identify enlarged nodes only. We also agree with the reviewer that a node dissection is not without associated morbidity and this must therefore be judged on a case by case basis. We have made amendments to the text in lines 275 onwards to give clarity on this.
We thank the reviewer for the opportunity to discuss restaging surgery. We respectfully disagree with their comments, with only sparse data in the literature in this regard. Given the overall good prognosis of BOT demonstrating survival differences is difficult. Data from the largest and most recent study in the literature (AGO) demonstrate a significant increase in the risk of recurrence with each staging step omitted 5. We agree that in cases where thorough exploration of the abdominal cavity has been undertaken at primary surgery then restaging is unlikely to significantly alter management, however in those women with an incidental finding of BOT following surgery by a non-gynaecological oncologist when complete abdominal exploration and staging was not performed at primary surgery a restaging procedure should be recommended. With regard to completion surgery, while no evidence suggests an improvement in prognosis in our experience this discussion is often raised by patients due to psychological stress and anxiety on completion of their family. We have added additional text for further clarity from line 282.

We thank you for your further consideration of our manuscript for publication in your journal. We have amended the manuscript in light of the reviewer's helpful comments and believe, given the lack of RCT's in BOT, data from our large case series is a significant addition to the literature. Our series add to the limited data available and supports counselling and decision making for clinicians, often non-gynaecological oncologists, in the management of BOT.

Yours sincerely

James MayRachel O'Donnell

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Title: Borderline ovarian tumours: Fifteen years' experience at a Scottish tertiary cancer centre

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Disclosures:

None of the authors have any conflict of interest to declare.

Ethical approval

Not applicable.

Funding

Not applicable.

Borderline ovarian tumours: Fifteen years' experience at a Scottish tertiary cancer centre

Highlights

- Management of borderline ovarian tumours is highly heterogeneous owing to variable patient, clinician and histological factors
- Extent of staging at primary surgery is variable, rates of secondary completion staging are often low and follow-up is highly variable
- Rates of recurrence and malignant transformation are exceptionally low but are higher with incomplete staging or incomplete resection

Borderline ovarian tumours: Fifteen years' experience at a Scottish tertiary cancer centre

Precis

Borderline ovarian tumours constitute a diverse range of tumours with variable behaviour. Uncertainty exists regarding their optimal management. This study represents the largest UK study describing the challenges of management and follow up.

Prof. Uziel Beller

Editor in Chief, International Journal of Gynaecological Cancer

9th July 2018

Dear Professor Beller,

We thank the reviewer for their comments regarding our manuscript 'Borderline ovarian tumours: Fifteen years' experience at a Scottish tertiary cancer centre'. We have considered the comments and have amended the manuscript accordingly. In response to the questions posed by the reviewer:

The results show a very high rate of laparotomy compared to laparoscopy: 90% versus 10%. How do the authors explain this rate?

1. We agree that the laparotomy rate in this series was higher (90%) than reported by other groups. The proportion of patients undergoing laparoscopy increased over the 15- year period, rising from 3% in the first 5 years to 16% in the final 5 years reflecting a growing acceptance of the safety of this approach between 2000 - 2015. The high rate of laparotomy may also be a reflection of the relatively high median diameter of tumours (16.5 cm) in this cohort compared to those reported in the literature examining laparoscopic management of BOT (7.5 cm) and concern regarding rupture and extraction of such large volume tumours [1]. Previous series examining cyst diameter have suggested that laparoscopic management might be restricted to low volume cysts [2]. We have added explanation of this to the discussion in lines 206-215.

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Borderline ovarian tumours: Fifteen years' experience at a Scottish tertiary cancer centre

Abstract

Objectives

Since the recognition of borderline ovarian tumours (BOT) in the 1970's the management of this subset of epithelial ovarian tumours has presented a challenge to clinicians. The majority present at an early stage but their diagnosis is often only made following surgery, hence the heterogeneity of surgical management. BOT are morphologically diverse, and their behaviour is subsequently also heterogeneous. We aimed to assess recurrence rates and the rate of malignant transformation in patients diagnosed with BOT. Secondary objectives included a review of current management and assessment of tumour markers, stage, cyst dimensions and the presence of micro-papillary features as prognostic indicators of recurrence.

Methods

This retrospective cohort study included all patients treated with BOT between 2000 and 2015 in the South-east region of Scotland. Clinical, surgicopathological and follow-up data were collated. Data were analysed with reference to recurrence and malignant transformation.

Results

275 patients underwent treatment for BOT in the study period. Surgical management was highly variable. A diagnosis of recurrent/persistent BOT or ovarian malignancy following initial treatment of BOT was rare with only 12/275 (4%) cases. There were 7 (3%) cases of ovarian malignancy. Advanced FIGO stage was the most prominent prognostic factor. Elevated pre-operative serum CA125 and the presence of micro-papillary features correlated with advanced stage at presentation. With a lack of clear guidance, follow up was highly variable with a median of 43 months (0 - 136).

Conclusions

To our knowledge this study is the largest BOT cohort in the UK. Recurrent disease is rare in optimally staged, completely resected, early stage BOT, without high risk features. Caution is needed in women electing not to undergo completion staging after diagnosis and in those opting for a fertility-preserving

approach. Thorough informed consent and clear plans for surveillance and follow-up are needed with consideration of delayed completion surgery as appropriate.

Word count: 298

Keywords:

Borderline ovarian tumours

Ovarian tumours of low malignant potential

Prognosis

Recurrence / relapse

Malignant transformation

Introduction

Borderline ovarian tumours (BOT) or tumours of low malignant potential, first described by Taylor in 1929 [1], account for 10 - 15% of all epithelial ovarian tumours. Characterised by cellular features of malignancy, they do not show destructive stromal invasion and thus fall short of the criteria of invasive cancer [2-4]. BOTs are one of the more controversial topics in gynaecology oncology given that their behaviour is not always entirely benign. The management and follow-up of this subset of epithelial ovarian tumours presents a challenge to clinicians with few clinical studies in recent decades to address these. There is clear guidance for the investigation and management of invasive ovarian cancer [5] but guidance for the management of BOT is less well established due to a relative paucity of evidence. In the 2010 Cochrane review, only 7 trials were evaluated with only one including a comparison of surgical approaches [6]. Debate persists regarding conservative surgical approaches, surveillance and the role of delayed completion surgery. Consequently, surgical approaches continue to vary due to individual surgeon opinion, patient preference and the broad spectrum of histological findings within this subset of ovarian tumours.

BOT cannot reliably be differentiated from benign or malignant disease pre-operatively. Subsequently, a range of specialists are involved in the provision of care, contributing to highly variable management. Historically, BOT had been described as a precursor of ovarian carcinoma and was consequently treated in the same way in an attempt to avoid recurrent invasive disease [7]. During recent decades, many observational studies have shown a radical operative approach, including lymphadenectomy, does not offer significant advantage in terms of relapse or survival [8,9]. Several studies have concluded that fertility sparing surgery may be appropriate for some patients[10,11], though a small, well-defined risk of recurrence persists in women treated conservatively [12-14].

The 10-year survival is reported to be 99% for stage I, 98% for stage II, 96% for stage III and 77% for stage IV [14-18]. Whilst the prognosis can be seen to be favourable in the majority, a proportion of women do succumb to their disease and therefore provision of accurate counselling and correct management is critical.

In the absence of a randomised controlled trial to address these many unanswered questions regarding optimum management of BOT we rely upon data from case series to facilitate appropriate counselling of patients. This study aimed to report the rate of recurrence and malignant transformation in a large series of BOT patients over a 15-year period in Scotland to define prognostic indicators of recurrence to guide follow-up protocol.

Materials and Methods

The Southeast of Scotland Cancer Network (SCAN) is centred on the Royal Infirmary of Edinburgh, UK, the major gynaecological oncology centre for the south-east region of Scotland, serving a population of 1.4 million. This observational study included all patients with pathologically proven BOT diagnosed between 2000 and 2015. Patients were prospectively registered on the SCAN database. As a service evaluation this study is exempt from the requirement for research ethical review.

BOT were defined using four histological characteristics [19]: (i) epithelial proliferation with/without the formation of microscopic papillary projections; (ii) atypical epithelial activity with no more than 4 mitotic figures per 10 high power field [20]; (iii) mild or moderate atypicality of the nuclei; (iv) isolated eosinophilic cells or cells clusters within the stroma, resembling the epithelial cells lining the surface of papillae, not exceeding 5mm in the largest diameter [21]. Lymph node involvement was defined as one or more lymph nodes containing a borderline epithelial proliferation closely resembling the BOT without invasion of the capsule [19]. Patients with invasive deposits were excluded in keeping with current classification of these tumours as low-grade serous carcinoma [21]. All patients underwent central pathological review.

Clinical, surgicopathological, follow-up and survival data were collated from the MDT database, patient medical records, pathology database and Information Services Division Scotland. Histopathological data included FIGO stage (1998), subtype, cyst dimensions and volume. Volume (V) was calculated using the following equation: $V = (l \times w \times d) \times 0.523$ where l, w, and d are the geometric length, width, and depth of

the cyst, respectively. Primary treatment was defined as treatment before or immediate treatment after referral to SCAN.

Staging was considered complete if surgery included bilateral salpingo-oophorectomy (BSO), omental and peritoneal biopsies, cytology and, in cases of mucinous BOT (MBOT), appendicectomy. Hysterectomy and lymphadenectomy were not considered necessary for complete staging as per British Gynaecological Cancer Society guidelines [5].

Recurrence was defined as histological evidence of a tumour resembling the original pathology without invasion more than 6 months following primary surgery and malignant transformation as a tumour resembling the original pathology with invasion or distant metastases more than 6 months following primary surgery. Progression free survival (PFS) and overall survival (OS) were calculated from the date of diagnosis. Fisher's exact test was used to compare categorical variables. Continuous variables were compared using the Student's t test. Pearson's correlation coefficient was used to determine two-way linear associations. All statistical analysis was performed using GraphPad Prism Software (Version 7.03 for Windows, La Jolla, California, USA).

Results

In total 275 patients were treated for BOT during the study period. The median age at diagnosis was 52 years (17 – 88). 130 (47%) patients were pre-menopausal, of which 42 (32%) were nulliparous. 229 (83%) patients presented with clinical symptoms, the remainder (16%) were diagnosed incidentally during unrelated medical investigations. All patients underwent primary surgical treatment (90% laparotomy, 10% laparoscopy). (Table 1).

Most tumours were of an MBOT subtype (155/275, 56%) with 111 (40%) reported as serous borderline (SBOT). There were 3 (1%) cases of endometrioid BOT (EBOT), 4 were classified as mixed seromucinous (mxBOT) type and two without clear classification. Tumours were bilateral in 45 (16%) cases, of which 40 (89%) cases were SBOT. More than 80% (228/275) of tumours were diagnosed at early stage (≤ FIGO

Stage1C), 4% (11/275) Stage 2, 8% (21/275) Stage 3 and 1 case of Stage 4 disease. Cysts varied greatly in size with a median cyst diameter of 16.5 cm (3 – 50 cm). Median cyst diameter was higher in MBOT (20 cm) than SBOT (11 cm), ($p<0.0001$). Cyst volume was also highly variable with a median of 585 cm^3, (2 - 16,631 cm^3). Median cyst volume was higher in MBOT (971 cm^3) than SBOT (181 cm^3), ($p=0.0013$). Pre-operative CA125 was higher for SBOT (median, 73 KU/L) in comparison to MBOT (median, 32 KU/L), ($p<0.001$), Figure 1, A.

The extent of surgery was highly variable. Ovarian function was preserved in 58 (21%) patients of whom 11 (19%) underwent ovarian cystectomy and the remainder unilateral salpingo-oophorectomy (USO). Staging was complete at primary surgery in 94/275 (34%) cases. This varied according to histology with 60% (67/111) of women with SBOT completely staged at primary surgery compared to 16% (25/155) patients with MBOT and 67% (2/3) EBOT. Only 25/155 (16%) of MBOT underwent appendicectomy. Secondary procedures for purposes of completion staging were undertaken in 24 patients following which staging was complete in 104/275 (38%) cases. Ten patients underwent second surgical procedures for suspected recurrence of which 7 were confirmed as recurrent disease and 3 benign. One patient received adjuvant chemotherapy (6 cycles of carboplatin and paclitaxel) after complete staging surgery for a FIGO stage 3C SBOT with non-invasive implants, following review at the gynaecology oncology MDT.

Recurrent or persistent BOT as well as malignant transformation, following initial treatment of BOT, was identified in 12/275 (4%) cases (Ttable 21). Median PFS was 14 months (1 - 36). Four patients developed recurrent borderline disease (3 SBOT, 1 MBOT), all were asymptomatic. Three cases were diagnosed on clinical examination or ultrasound during routine follow up, one was an incidental finding at the time of a hernia repair. One further patient was considered to have persistent disease, presenting with abdominal pain 3 months post operatively following surgery for FIGO stage 3A SBOT with residual disease described at initial surgery. All 5 patients were managed surgically and had no further episodes of disease recurrence with median FU of 43 months (32 - 201).

Seven patients were diagnosed with an ovarian malignancy following an initial diagnosis of BOT of which 5 died during follow up (Table 2). The median OS in this group was 50 months (8 - 136). All patients presented symptomatically. Not all cases can be easily classified as recurrent disease or malignant transformation arising from BOT. Two patients presented within 6 months of primary surgery, both had equivocal original pathology and although formerly classified as a BOT, they were acknowledged to be at least at the malignant end of the continuous spectrum of BOT. One patient was incompletely staged and the other had residual disease following primary surgery. Two ovarian malignancies were diagnosed, for which BOT is not recognised to be a precursor lesion. One patient, diagnosed with FIGO stage 1A MBOT following USO (with biopsy of contralateral, omental biopsy, lymph node sampling and appendicectomy), presented with disseminated Sertoli Leydig tumour 7 months postoperatively. Another patient, found to have an incidental, unilateral SBOT following risk reducing BSO for a BRCA1 mutation, was later diagnosed with high grade serous primary peritoneal carcinoma.

There was positive correlation between pre-operative CA125 and increasing FIGO stage of tumour, Figure 1, B, ($r = 0.182$, $p=0.005$). CEA was significantly higher in MBOT in comparison to the serous subtypes ($p=0.008$). There was no significant correlation between CEA and FIGO stage ($r = 0.072$, $p=0.468$), Figure 1, C and D. There was positive correlation between FIGO stage at presentation and risk of recurrent/persistent disease ($r=0.236$, $p=0.0002$) and positive correlation between the presence of micro-papillary features on histology and FIGO stage of disease ($r=0.993$, $p=0.073$), **Error! Reference source not found.** Micro-papillary features were no more prevalent (4/12, 33%) in patients who recurred in comparison to patients without documented recurrence (75/263, 29%), ($p=0.748$). Micro-invasion was seen in 1/12 (8%) of those cases who recurred in comparison to 12/263 (5%) of those that who did not ($p=0.446$). A correlation of $r=0.844$ ($p=0.360$) was seen between presence of micro-invasion and stage of disease. Preservation of ovarian function was more common in patients who recurred ($p=0.039$).

The duration and frequency of follow-up was not consistent with substantial variation. Median follow-up for the entire cohort was 43 months (0 – 136). Twenty-three (8%) patients had no follow-up and were

discharged to their GP immediately following surgery. Eighteen remain alive with no recurrent disease identified, the remaining 5 died of causes unrelated to BOT.

Discussion

This study represents the largest UK series of BOT and in addition to providing valuable data, highlights the lack of consensus about both treatment and follow-up resulting in variability of surgical management and post-operative follow-up. While the retrospective nature of our data is acknowledged as a limitation, it offers the opportunity to reflect on the changing nature of practice within the 15-year study period.

In our study, stage at presentation was correlated with risk of recurrence. The number of patients completely staged at primary surgery was low (34%). Only 24 women underwent secondary surgery for completion of staging. Due to the retrospective nature of the study it was difficult to determine if the low rate of secondary surgery was due to patient choice or variation in management between individual surgeons. Secondary surgery for staging purposes exposes patients to further surgical and anaesthetic risk, yet omission of thorough staging, particularly in women undergoing fertility sparing surgery, precludes valuable prognostic information. Data from the AGO ROBOT study demonstrated the importance of complete staging, with an increase in recurrence risk for each surgical staging step omitted [22]. In our study, the most commonly omitted step in staging was appendicectomy with only 16% of women with MBOT undergoing this procedure. While appendicectomy is commonly performed in the staging of MBOT, data from several studies do not support this practice in the presence of a macroscopically normal appendix [23,24]. ~~The value of secondary surgery for the purposes of appendicectomy alone is therefore unclear~~.

Intraoperative frozen section, not utilised in this cohort as this service was not routinely available throughout this series (2000 - 2015), has been demonstrated to have reasonable specificity in the diagnosis of BOT. The additional resources needed for frozen section must be considered but may be offset by the potential reduction in the need for secondary staging surgery in patients with invasive and borderline disease, particularly when a conservative approach is desired. It must be acknowledged that a significant proportion of women thought to have borderline disease on frozen section will be classified as

malignant on final pathology creating potential for under staging in serous malignant disease if lymphadenectomy is not undertaken [25,26]. Complex decisions regarding loss of fertility in premenopausal women are therefore preferably made following accurate diagnosis based upon formal pathology review of paraffin embedded material and we would encourage a 2-step procedure in such patients to ensure adequate and specific counselling.

While the laparoscopic approach to BOT has not been evaluated in a randomized trial, evidence from retrospective series suggest that a laparoscopic approach is not associated with an increase in the risk of recurrence [27]. The number of patients undergoing laparotomy in this series was higher (90%) than reported by other groups [28]. The proportion of patients undergoing laparoscopy increased over the 15- year period, rising from 3% in the first 5 years to 16% in the final 5 years reflecting acceptance of the safety of this approach. The high rate of laparotomy may reflect the relatively high median diameter of tumours (16.5 cm) in this cohort compared to those reported in the literature examining laparoscopic management of BOT (7.5 cm) [27] and concern regarding rupture and extraction of such large volume tumours. Previous series examining cyst diameter have suggested that laparoscopic management might be restricted to low volume cysts [29].

In this study, 12% of women were aged 40 years or younger and nulliparous at the time of diagnosis, representing a sub population in whom potential randomisation in the setting of a clinical trial presents clear difficulties. Consistent with published data, ovarian preservation was more prevalent in women who subsequently developed recurrent disease compared those that did not. Relapse rates are reported to be higher after cystectomy (12 – 58%) and unilateral salpingo-oophorectomy (0 – 20%) compared with patients who have undergone complete staging surgery (2.5 – 5.7%) [30]. There is little published to address the rate of conception and live birth rate following conservative management of BOT. Palomba et al reported a significantly higher conception rate in women undergoing bilateral cystectomy for bilateral SBOT in comparison to USO and contralateral cystectomy [31]. After 128 months of follow up, patients treated with the more conservative approach had improved outcomes in terms of live birth rates, however there was a significantly shorter time to relapse and need for completion surgery. No significant difference in the number of recurrences was identified and no deaths occurred [11].

The overall rate of malignant relapse was 3% in our series; this is in keeping with du Bois et al who reported malignant relapse in 2.3% of a series of 950 patients [32]. The risk of recurrence and malignant transformation is highly variable between studies with a reported mean of 3% ranging from 0 – 58% [33]. This may in part be due to the inconsistent approach to completion surgery for staging and the recognised intra-/inter-observer variation in the histological reporting of BOT emphasising the importance of central pathological review by an expert gynaecological pathologist [34].

This study supports available evidence regarding prognostic indicators for risk of recurrence/malignant transformation. Advanced FIGO stage was the most prominent prognostic factor identified. Micropapillary features and microinvasion were not independently associated with increased recurrence risk. The presence of micro-papillary features was correlated with advanced stage at presentation. There was a significant correlation between elevated CA125 and stage at presentation. Advanced FIGO stage, microinvasion, presence of implants, as well as micropapillary pattern have been reported by some as risk factors for extra-ovarian disease and recurrence, but this is not consistent in the literature [35-38]. These features should be used for the identification of women at highest risk of recurrence facilitating provision of appropriate counselling, consideration of completion surgery and/or close follow-up. Conversely, fertility sparing surgery should be reserved for women with early stage disease in the absence of poor prognostic indicators with the option of staging surgery following completion of a family.

The follow up of patients within this series was highly variable perhaps reflecting the lack of national consensus regarding optimal practice. In the changing face of traditional hospital based follow up in the UK, with a move towards patient-led, non-hospital based follow-up programmes; individualised strategies based on available prognostic information may be required. Patients with advanced stage disease and women in whom complete staging has not been performed require close surveillance. In our study, all patients subsequently diagnosed with malignancy, presented symptomatically. Detection of asymptomatic recurrence by transvaginal ultrasound has been demonstrated by several authors [11]. In one case series follow-up ultrasound detected the abnormality in all patients in whom recurrence occurred (n=28) [12]. These

recurrences were associated with an abnormal physical vaginal examination in 57% of cases and an elevated CA125 in 33% [12,33]. Recurrent borderline disease that is detected early is usually easily resectable and consequently carries an excellent prognosis [39]. In our series, 3 women underwent surgery for presumed recurrence which was confirmed as benign disease. The potential for intensive surveillance to increase intervention for benign disease should be considered along with the resource implications of repeated imaging. Recurrences as late as 23 and 25 years after initial diagnosis have been reported and the optimum duration of follow up is not clear [40]. In women with Stage 1A/1B disease with optimal surgery and the absence of high risk prognostic factors, recurrence is rare, and consideration should be given to discharge from long-term follow-up, after discussion with the patient. For women with FIGO stage 1C or above, those in whom staging has been incomplete or where fertility has been conserved, long-term follow-up should be recommended which may include ultrasound, CA125 and clinical examination. The linear pattern of recurrence described in some studies suggests that an intense follow-up regimen may not be needed and with a lack of evidence to dictate best practice, annual follow-up may be appropriate.

We propose that all cases of BOT are discussed at a tertiary cancer centre including central review of pathology. Where possible patients with moderate or high RMI should have surgery undertaken in a tertiary cancer centre where full surgical staging can be undertaken. The availability of intra-operative frozen section should be used where available to guide the extent of excision/staging undertaken at initial surgery. A frozen section result demonstrating BOT should prompt complete staging ~~including consideration of lymph node assessment in non-mucinous disease, and appendicectomy in MBOT.[5].~~ ~~Although~~ No survival benefit has been shown with lymphadenectomy in BOT and systematic lymphadenectomy or lymph node sampling should not be routinely performed. Intraoperative examination of lymph nodes should be considered such that, in accordance with current UK guidelines [5], enlarged lymph nodes only may be removed~~,~~ ~~lymph node assessment .~~ [5]~~would ensure that cases of early invasive disease are fully staged [41].~~ Secondary surgery for restaging, if the initial operation was incomplete,~~ should be recommended~~ requires careful counselling. Several studies indicate an inferior outcome in inadequately staged patients [27,28]. Data from the AGO ROBOT study highlight an increase in the recurrence risk for each staging procedure omitted with 14.6% of patients upstaged following restaging procedures [22]. While retrospective series have

suggested that restaging does not have a significant impact on patient management having failed to demonstrate any improvement in overall survival [42] others suggest restaging is associated with improved PFS in higher risk cohorts [43]. Restaging surgery is most relevant to those women with an incidental finding of BOT following surgery by a non-gynaecological oncologist when complete abdominal exploration and staging was not performed at primary surgery and should be recommended in these circumstances.

Completion surgery in women undergoing fertility preservation ~~should~~ may be discussed when fertility is no longer desired although it should be emphasised that there are no data suggesting this impacts on overall survival or progression free survival. Decisions regarding secondary surgery and surgery in the context of fertility preservation are complex and recruitment to a prospective randomised trial presents significant difficulties. Given the variation in current practice, publication of data from other UK centres would allow meta-analysis of larger numbers, providing more robust data to guide patient counselling and decision making. We therefore propose the initiation of a UK wide database to help inform future patient care.

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Legends to figures and tables

Figure 1: CA125 and CEA levels by histological subtype and correlation with FIGO stage

Figure 2:Correlation between micropapillary features and FIGO stage of borderline ovarian tumour at presentation

Table 1: Cohort demographics

Table ~~1~~2: Detailed patient demographics of 12 patients with recurrent BOT or malignant transformation

Borderline ovarian tumours: Fifteen years' experience at a Scottish tertiary cancer centre

Abstract

Objectives

Since the recognition of borderline ovarian tumours (BOT) in the 1970's the management of this subset of epithelial ovarian tumours has presented a challenge to clinicians. The majority present at an early stage but their diagnosis is often only made following surgery, hence the heterogeneity of surgical management. BOT are morphologically diverse, and their behaviour is subsequently also heterogeneous. We aimed to assess recurrence rates and the rate of malignant transformation in patients diagnosed with BOT. Secondary objectives included a review of current management and assessment of tumour markers, stage, cyst dimensions and the presence of micro-papillary features as prognostic indicators of recurrence.

Methods

This retrospective cohort study included all patients treated with BOT between 2000 and 2015 in the South-east region of Scotland. Clinical, surgicopathological and follow-up data were collated. Data were analysed with reference to recurrence and malignant transformation.

Results

275 patients underwent treatment for BOT in the study period. Surgical management was highly variable. A diagnosis of recurrent/persistent BOT or ovarian malignancy following initial treatment of BOT was rare with only 12/275 (4%) cases. There were 7 (3%) cases of ovarian malignancy. Advanced FIGO stage was the most prominent prognostic factor. Elevated pre-operative serum CA125 and the presence of micro-papillary features correlated with advanced stage at presentation. With a lack of clear guidance, follow up was highly variable with a median of 43 months (0 - 136).

Conclusions

To our knowledge this study is the largest BOT cohort in the UK. Recurrent disease is rare in optimally staged, completely resected, early stage BOT, without high risk features. Caution is needed in women electing not to undergo completion staging after diagnosis and in those opting for a fertility-preserving

approach. Thorough informed consent and clear plans for surveillance and follow-up are needed with consideration of delayed completion surgery as appropriate.

Word count: 298

Keywords:

Borderline ovarian tumours

Ovarian tumours of low malignant potential

Prognosis

Recurrence / relapse

Malignant transformation

Introduction

Borderline ovarian tumours (BOT) or tumours of low malignant potential, first described by Taylor in 1929 [1], account for 10 - 15% of all epithelial ovarian tumours. Characterised by cellular features of malignancy, they do not show destructive stromal invasion and thus fall short of the criteria of invasive cancer [2-4]. BOTs are one of the more controversial topics in gynaecology oncology given that their behaviour is not always entirely benign. The management and follow-up of this subset of epithelial ovarian tumours presents a challenge to clinicians with few clinical studies in recent decades to address these. There is clear guidance for the investigation and management of invasive ovarian cancer [5] but guidance for the management of BOT is less well established due to a relative paucity of evidence. In the 2010 Cochrane review, only 7 trials were evaluated with only one including a comparison of surgical approaches [6]. Debate persists regarding conservative surgical approaches, surveillance and the role of delayed completion surgery. Consequently, surgical approaches continue to vary due to individual surgeon opinion, patient preference and the broad spectrum of histological findings within this subset of ovarian tumours.

BOT cannot reliably be differentiated from benign or malignant disease pre-operatively. Subsequently, a range of specialists are involved in the provision of care, contributing to highly variable management. Historically, BOT had been described as a precursor of ovarian carcinoma and was consequently treated in the same way in an attempt to avoid recurrent invasive disease [7]. During recent decades, many observational studies have shown a radical operative approach, including lymphadenectomy, does not offer significant advantage in terms of relapse or survival [8,9]. Several studies have concluded that fertility sparing surgery may be appropriate for some patients[10,11], though a small, well-defined risk of recurrence persists in women treated conservatively [12-14].

The 10-year survival is reported to be 99% for stage I, 98% for stage II, 96% for stage III and 77% for stage IV [14-18]. Whilst the prognosis can be seen to be favourable in the majority, a proportion of women do succumb to their disease and therefore provision of accurate counselling and correct management is critical.

In the absence of a randomised controlled trial to address these many unanswered questions regarding optimum management of BOT we rely upon data from case series to facilitate appropriate counselling of patients. This study aimed to report the rate of recurrence and malignant transformation in a large series of BOT patients over a 15-year period in Scotland to define prognostic indicators of recurrence to guide follow-up protocol.

Materials and Methods

The Southeast of Scotland Cancer Network (SCAN) is centred on the Royal Infirmary of Edinburgh, UK, the major gynaecological oncology centre for the south-east region of Scotland, serving a population of 1.4 million. This observational study included all patients with pathologically proven BOT diagnosed between 2000 and 2015. Patients were prospectively registered on the SCAN database. As a service evaluation this study is exempt from the requirement for research ethical review.

BOT were defined using four histological characteristics [19]: (i) epithelial proliferation with/without the formation of microscopic papillary projections; (ii) atypical epithelial activity with no more than 4 mitotic figures per 10 high power field [20]; (iii) mild or moderate atypicality of the nuclei; (iv) isolated eosinophilic cells or cells clusters within the stroma, resembling the epithelial cells lining the surface of papillae, not exceeding 5mm in the largest diameter [21]. Lymph node involvement was defined as one or more lymph nodes containing a borderline epithelial proliferation closely resembling the BOT without invasion of the capsule [19]. Patients with invasive deposits were excluded in keeping with current classification of these tumours as low-grade serous carcinoma [21]. All patients underwent central pathological review.

Clinical, surgicopathological, follow-up and survival data were collated from the MDT database, patient medical records, pathology database and Information Services Division Scotland. Histopathological data included FIGO stage (1998), subtype, cyst dimensions and volume. Volume (V) was calculated using the following equation: $V = (l \times w \times d) \times 0.523$ where l, w, and d are the geometric length, width, and depth of

the cyst, respectively. Primary treatment was defined as treatment before or immediate treatment after referral to SCAN.

Staging was considered complete if surgery included bilateral salpingo-oophorectomy (BSO), omental and peritoneal biopsies, cytology and, in cases of mucinous BOT (MBOT), appendicectomy. Hysterectomy and lymphadenectomy were not considered necessary for complete staging as per British Gynaecological Cancer Society guidelines [5].

Recurrence was defined as histological evidence of a tumour resembling the original pathology without invasion more than 6 months following primary surgery and malignant transformation as a tumour resembling the original pathology with invasion or distant metastases more than 6 months following primary surgery. Progression free survival (PFS) and overall survival (OS) were calculated from the date of diagnosis. Fisher's exact test was used to compare categorical variables. Continuous variables were compared using the Student's t test. Pearson's correlation coefficient was used to determine two-way linear associations. All statistical analysis was performed using GraphPad Prism Software (Version 7.03 for Windows, La Jolla, California, USA).

Results

In total 275 patients were treated for BOT during the study period. The median age at diagnosis was 52 years (17 – 88). 130 (47%) patients were pre-menopausal, of which 42 (32%) were nulliparous. 229 (83%) patients presented with clinical symptoms, the remainder (16%) were diagnosed incidentally during unrelated medical investigations. All patients underwent primary surgical treatment (90% laparotomy, 10% laparoscopy), (Table 1).

Most tumours were of an MBOT subtype (155/275, 56%) with 111 (40%) reported as serous borderline (SBOT). There were 3 (1%) cases of endometrioid BOT (EBOT), 4 were classified as mixed seromucinous (mxBOT) type and two without clear classification. Tumours were bilateral in 45 (16%) cases, of which 40 (89%) cases were SBOT. More than 80% (228/275) of tumours were diagnosed at early stage (≤ FIGO

Stage1C), 4% (11/275) Stage 2, 8% (21/275) Stage 3 and 1 case of Stage 4 disease. Cysts varied greatly in size with a median cyst diameter of 16.5 cm (3 – 50 cm). Median cyst diameter was higher in MBOT (20 cm) than SBOT (11 cm), ($p<0.0001$). Cyst volume was also highly variable with a median of 585 cm^3, (2 - 16,631 cm^3). Median cyst volume was higher in MBOT (971 cm^3) than SBOT (181 cm^3), ($p=0.0013$). Pre-operative CA125 was higher for SBOT (median, 73 KU/L) in comparison to MBOT (median, 32 KU/L), ($p<0.001$), Figure 1, A.

The extent of surgery was highly variable. Ovarian function was preserved in 58 (21%) patients of whom 11 (19%) underwent ovarian cystectomy and the remainder unilateral salpingo-oophorectomy (USO). Staging was complete at primary surgery in 94/275 (34%) cases. This varied according to histology with 60% (67/111) of women with SBOT completely staged at primary surgery compared to 16% (25/155) patients with MBOT and 67% (2/3) EBOT. Only 25/155 (16%) of MBOT underwent appendicectomy. Secondary procedures for purposes of completion staging were undertaken in 24 patients following which staging was complete in 104/275 (38%) cases. Ten patients underwent second surgical procedures for suspected recurrence of which 7 were confirmed as recurrent disease and 3 benign. One patient received adjuvant chemotherapy (6 cycles of carboplatin and paclitaxel) after complete staging surgery for a FIGO stage 3C SBOT with non-invasive implants, following review at the gynaecology oncology MDT.

Recurrent or persistent BOT as well as malignant transformation, following initial treatment of BOT, was identified in 12/275 (4%) cases (Table 2). Median PFS was 14 months (1 - 36). Four patients developed recurrent borderline disease (3 SBOT, 1 MBOT), all were asymptomatic. Three cases were diagnosed on clinical examination or ultrasound during routine follow up, one was an incidental finding at the time of a hernia repair. One further patient was considered to have persistent disease, presenting with abdominal pain 3 months post operatively following surgery for FIGO stage 3A SBOT with residual disease described at initial surgery. All 5 patients were managed surgically and had no further episodes of disease recurrence with median FU of 43 months (32 - 201).

Seven patients were diagnosed with an ovarian malignancy following an initial diagnosis of BOT of which 5 died during follow up (Table 2). The median OS in this group was 50 months (8 - 136). All patients presented symptomatically. Not all cases can be easily classified as recurrent disease or malignant transformation arising from BOT. Two patients presented within 6 months of primary surgery, both had equivocal original pathology and although formerly classified as a BOT, they were acknowledged to be at least at the malignant end of the continuous spectrum of BOT. One patient was incompletely staged and the other had residual disease following primary surgery. Two ovarian malignancies were diagnosed, for which BOT is not recognised to be a precursor lesion. One patient, diagnosed with FIGO stage 1A MBOT following USO (with biopsy of contralateral, omental biopsy, lymph node sampling and appendicectomy), presented with disseminated Sertoli Leydig tumour 7 months postoperatively. Another patient, found to have an incidental, unilateral SBOT following risk reducing BSO for a BRCA1 mutation, was later diagnosed with high grade serous primary peritoneal carcinoma.

There was positive correlation between pre-operative CA125 and increasing FIGO stage of tumour, Figure 1, B, ($r = 0.182$, $p=0.005$). CEA was significantly higher in MBOT in comparison to the serous subtypes ($p=0.008$). There was no significant correlation between CEA and FIGO stage ($r = 0.072$, $p=0.468$), Figure 1, C and D. There was positive correlation between FIGO stage at presentation and risk of recurrent/persistent disease ($r=0.236$, $p=0.0002$) and positive correlation between the presence of micro-papillary features on histology and FIGO stage of disease ($r=0.993$, $p=0.073$), **Error! Reference source not found.** Micro-papillary features were no more prevalent (4/12, 33%) in patients who recurred in comparison to patients without documented recurrence (75/263, 29%), ($p=0.748$). Micro-invasion was seen in 1/12 (8%) of those cases who recurred in comparison to 12/263 (5%) of those that who did not ($p=0.446$). A correlation of $r=0.844$ ($p=0.360$) was seen between presence of micro-invasion and stage of disease. Preservation of ovarian function was more common in patients who recurred ($p=0.039$).

The duration and frequency of follow-up was not consistent with substantial variation. Median follow-up for the entire cohort was 43 months (0 – 136). Twenty-three (8%) patients had no follow-up and were

discharged to their GP immediately following surgery. Eighteen remain alive with no recurrent disease identified, the remaining 5 died of causes unrelated to BOT.

Discussion

This study represents the largest UK series of BOT and in addition to providing valuable data, highlights the lack of consensus about both treatment and follow-up resulting in variability of surgical management and post-operative follow-up. While the retrospective nature of our data is acknowledged as a limitation, it offers the opportunity to reflect on the changing nature of practice within the 15-year study period.

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Intraoperative frozen section, not utilised in this cohort as this service was not routinely available throughout this series (2000 - 2015), has been demonstrated to have reasonable specificity in the diagnosis of BOT. The additional resources needed for frozen section must be considered but may be offset by the potential reduction in the need for secondary staging surgery in patients with invasive and borderline disease, particularly when a conservative approach is desired. It must be acknowledged that a significant proportion of women thought to have borderline disease on frozen section will be classified as malignant on final pathology creating potential for under staging in serous malignant disease if

lymphadenectomy is not undertaken [25,26]. Complex decisions regarding loss of fertility in premenopausal women are therefore preferably made following accurate diagnosis based upon formal pathology review of paraffin embedded material and we would encourage a 2-step procedure in such patients to ensure adequate and specific counselling.

While the laparoscopic approach to BOT has not been evaluated in a randomized trial, evidence from retrospective series suggest that a laparoscopic approach is not associated with an increase in the risk of recurrence [27]. The number of patients undergoing laparotomy in this series was higher (90%) than reported by other groups [28]. The proportion of patients undergoing laparoscopy increased over the 15- year period, rising from 3% in the first 5 years to 16% in the final 5 years reflecting acceptance of the safety of this approach. The high rate of laparotomy may reflect the relatively high median diameter of tumours (16.5 cm) in this cohort compared to those reported in the literature examining laparoscopic management of BOT (7.5 cm) [27] and concern regarding rupture and extraction of such large volume tumours. Previous series examining cyst diameter have suggested that laparoscopic management might be restricted to low volume cysts [29].

In this study, 12% of women were aged 40 years or younger and nulliparous at the time of diagnosis, representing a sub population in whom potential randomisation in the setting of a clinical trial presents clear difficulties. Consistent with published data, ovarian preservation was more prevalent in women who subsequently developed recurrent disease compared those that did not. Relapse rates are reported to be higher after cystectomy (12 – 58%) and unilateral salpingo-oophorectomy (0 – 20%) compared with patients who have undergone complete staging surgery (2.5 – 5.7%) [30]. There is little published to address the rate of conception and live birth rate following conservative management of BOT. Palomba et al reported a significantly higher conception rate in women undergoing bilateral cystectomy for bilateral SBOT in comparison to USO and contralateral cystectomy [31]. After 128 months of follow up, patients treated with the more conservative approach had improved outcomes in terms of live birth rates, however there was a significantly shorter time to relapse and need for completion surgery. No significant difference in the number of recurrences was identified and no deaths occurred [11].

The overall rate of malignant relapse was 3% in our series; this is in keeping with du Bois et al who reported malignant relapse in 2.3% of a series of 950 patients [32]. The risk of recurrence and malignant transformation is highly variable between studies with a reported mean of 3% ranging from 0 – 58% [33]. This may in part be due to the inconsistent approach to completion surgery for staging and the recognised intra-/inter-observer variation in the histological reporting of BOT emphasising the importance of central pathological review by an expert gynaecological pathologist [34].

This study supports available evidence regarding prognostic indicators for risk of recurrence/malignant transformation. Advanced FIGO stage was the most prominent prognostic factor identified. Micropapillary features and microinvasion were not independently associated with increased recurrence risk. The presence of micro-papillary features was correlated with advanced stage at presentation. There was a significant correlation between elevated CA125 and stage at presentation. Advanced FIGO stage, microinvasion, presence of implants, as well as micropapillary pattern have been reported by some as risk factors for extra-ovarian disease and recurrence, but this is not consistent in the literature [35-38]. These features should be used for the identification of women at highest risk of recurrence facilitating provision of appropriate counselling, consideration of completion surgery and/or close follow-up. Conversely, fertility sparing surgery should be reserved for women with early stage disease in the absence of poor prognostic indicators with the option of staging surgery following completion of a family.

The follow up of patients within this series was highly variable perhaps reflecting the lack of national consensus regarding optimal practice. In the changing face of traditional hospital based follow up in the UK, with a move towards patient-led, non-hospital based follow-up programmes; individualised strategies based on available prognostic information may be required. Patients with advanced stage disease and women in whom complete staging has not been performed require close surveillance. In our study, all patients subsequently diagnosed with malignancy, presented symptomatically. Detection of asymptomatic recurrence by transvaginal ultrasound has been demonstrated by several authors [11]. In one case series follow-up ultrasound detected the abnormality in all patients in whom recurrence occurred (n=28) [12]. These recurrences were associated with an abnormal physical vaginal examination in 57% of cases and an

elevated CA125 in 33% [12,33]. Recurrent borderline disease that is detected early is usually easily resectable and consequently carries an excellent prognosis [39]. In our series, 3 women underwent surgery for presumed recurrence which was confirmed as benign disease. The potential for intensive surveillance to increase intervention for benign disease should be considered along with the resource implications of repeated imaging. Recurrences as late as 23 and 25 years after initial diagnosis have been reported and the optimum duration of follow up is not clear [40]. In women with Stage 1A/1B disease with optimal surgery and the absence of high risk prognostic factors, recurrence is rare, and consideration should be given to discharge from long-term follow-up, after discussion with the patient. For women with FIGO stage 1C or above, those in whom staging has been incomplete or where fertility has been conserved, long-term follow-up should be recommended which may include ultrasound, CA125 and clinical examination. The linear pattern of recurrence described in some studies suggests that an intense follow-up regimen may not be needed and with a lack of evidence to dictate best practice, annual follow-up may be appropriate.

We propose that all cases of BOT are discussed at a tertiary cancer centre including central review of pathology. Where possible patients with moderate or high RMI should have surgery undertaken in a tertiary cancer centre where full surgical staging can be undertaken. The availability of intra-operative frozen section should be used where available to guide the extent of excision/staging undertaken at initial surgery. A frozen section result demonstrating BOT should prompt complete staging No survival benefit has been shown with lymphadenectomy in BOT and systematic lymphadenectomy or lymph node sampling should not be routinely performed. Intraoperative examination of lymph nodes should be considered such that, in accordance with current UK guidelines [5], enlarged lymph nodes only may be removed .

Secondary surgery for restaging, if the initial operation was incomplete, requires careful counselling. Several studies indicate an inferior outcome in inadequately staged patients [27,28]. Data from the AGO ROBOT study highlight an increase in the recurrence risk for each staging procedure omitted with 14.6% of patients upstaged following restaging procedures [22]. While retrospective series have suggested that restaging does not have a significant impact on patient management having failed to demonstrate any improvement in overall survival [41] others suggest restaging is associated with improved PFS in higher risk cohorts [42]. Restaging surgery is most relevant to those women with an incidental finding of BOT following

surgery by a non-gynaecological oncologist when complete abdominal exploration and staging was not performed at primary surgery and should be recommended in these circumstances.

Completion surgery in women undergoing fertility preservation may be discussed when fertility is no longer desired although it should be emphasised that there are no data suggesting this impacts on overall survival or progression free survival. Decisions regarding secondary surgery and surgery in the context of fertility preservation are complex and recruitment to a prospective randomised trial presents significant difficulties. Given the variation in current practice, publication of data from other UK centres would allow meta-analysis of larger numbers, providing more robust data to guide patient counselling and decision making. We therefore propose the initiation of a UK wide database to help inform future patient care.

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Legends to figures and tables

Figure 1: CA125 and CEA levels by histological subtype and correlation with FIGO stage

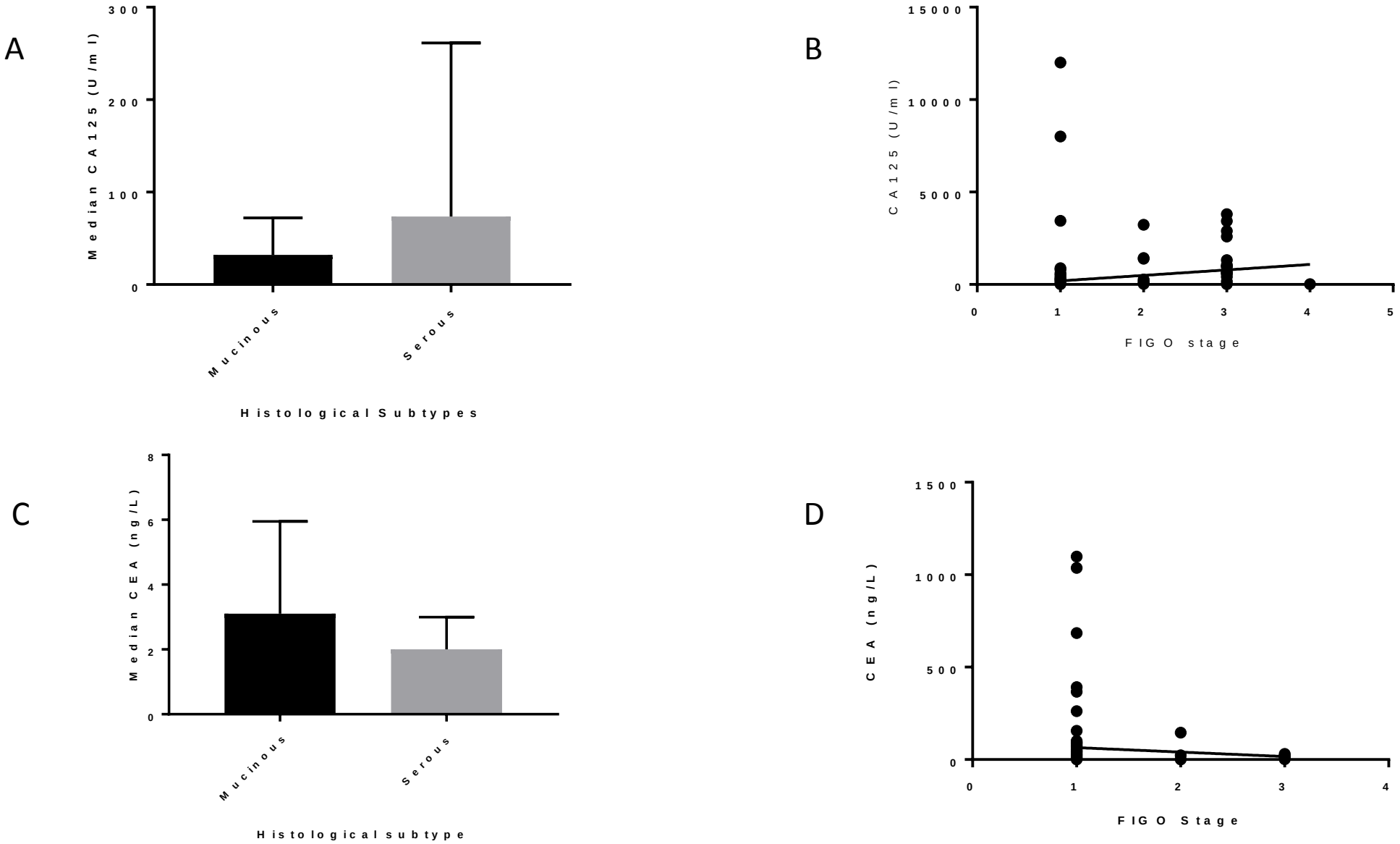
Figure 2:Correlation between micropapillary features and FIGO stage of borderline ovarian tumour at presentation

Table 1: Cohort demographics

Table 2: Detailed patient demographics of 12 patients with recurrent BOT or malignant transformation

Figure

Figure 1. CA125 and CEA levels by histological subtype and correlation with FIGO stage.



Figure

Figure 2: Correlation between micropapillary features and FIGO stage of disease at presentation

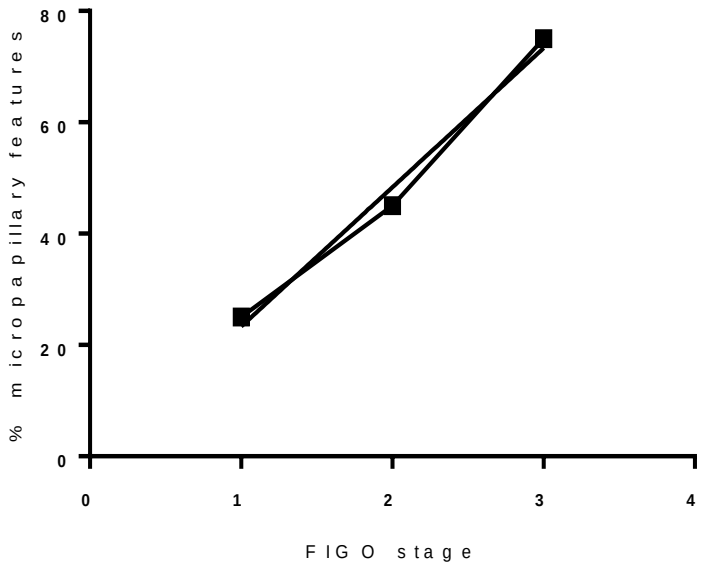


Table 1

Characteristics	n =275
Median age (range)	52 (17-88)
Histology	
Serous	111 (40%)
Mucinous	155 (56%)
Seromucinous	4 (1%)
Endometrioid	3 (1%)
Unclassified	2 (1%)
FIGO stage at Diagnosis	
I	228 (80%)
II	11 (4%)
III	21 (8%)
IV	1 (0.5%)
Histological Features	
Micropapillary features	79 (29%)
Microinvasion	13 (5%)
Surgical Approach	
Laparotomy	247 (90%)
Laparoscopy	28 (10%)
Complete staging at primary surgery	94 (34%)
Ovarian function preservation	58 (21%)
Ovarian cystectomy	11
Unilateral salpingo-oophorectomy	47
Surgical Procedures	
Ovarian cystectomy	11 (4%)
Unilateral salpingo-oophorectomy	71 (26%)
Bilateral salpingo-oophorectomy	190 (69%)
Hysterectomy	169 (61%)

Table 1. Baseline characteristics and surgical procedures

Table 2

Age (years)	Pre-operative CA125 (U/ ml)	Primary Surgery	Histological subtype	FIGO Stage	Micropapilliary features	Progression Free Survival (months)	Presentation of Recurrence	Recurrence/malignant transformation	Management	Patient status	Follow up (months)
Recurrent BOT											
45	Not done	STAH BSO	Serous	2C	Yes	36	Palpable pelvic mass on vaginal examination at routine follow-up 3 years post-op	SBOT	Laparotomy – excision of recurrent BOT	Alive	201
27	15	Left Ovarian Cystectomy	Serous	1C	No	30	Complex ovarian cystic structure on routine follow up pelvic ultrasound	SBOT	Laparotomy - Unilateral oophorectomy + omentectomy + biopsy of contralateral ovary	Alive	63
25	420	Unilateral oophorectomy, omentectomy, contralateral ovarian biopsy, pelvic peritonectomy (Residual disease)	Serous	3A	Yes	3 (Progressive disease)	MRI 1 month post-op: cystic mass	SBOT	Laparotomy - oophorectomy and excision of mass from pelvic side wall	Alive	32
44	355	Unilateral oophorectomy, omentectomy, contralateral ovarian biopsy	Serous	1C	No	36	Complex ovarian cystic structure on routine follow up pelvic ultrasound	SBOT	TLH, unilateral oophorectomy, omentectomy	Alive	43
47	78	TAH BSO omentectomy	Mucinous	1C	No	20	Incidental finding of ovarian remnant containing BOT at time of hernia repair	MBOT	No further treatment	Alive	32
Malignant Transformation											**Overall survival (months)**
39	263	Prophylactic BSO for BRCA1 carrier status	Serous	1A	Yes	8	Abdominal pain and distension	High Grade Serous Primary Peritoneal Carcinoma	Carbotaxol chemotherapy	Died of disease	58
53	3230	TAH, BSO, omentectomy (Residual disease)	Serous	2B	No	5 (Progressive disease)	Abdominal distension and pain	CT: disseminated malignancy	Carbotaxol chemotherapy	Died of disease	50
62	39	TAH BSO Omentectomy	Serous	3C	no	21	Abdominal pain and distension	Low grade serous carcinoma	Laparotomy - omentectomy, transverse colectomy, small bowel resection	Alive In remission	56
37	1060	Unilateral oophorectomy, omental biopsy (Equivocal original pathology)	Serous	3B	Yes	1 (Progressive disease)	Abdominal pain 1 month post-op	BOT with invasion	Laparotomy TAH, unilateral oophorectomy, omentectomy	Alive in remission	136
70	85	TAH BSO, omentectomy	Mucinous	1A	No	7	Abdominal pain	CT: disseminated malignancy	Carbotaxol chemotherapy	Died of disease	41
22	32	Unilateral oophorectomy, omental biopsy, contra-lateral ovarian biopsy, appendicectomy, para-aortic node sampling	Mucinous	1A	No	7	Abdominal distension during pregnancy	Sertoli-leydig tumour (Unrelated malignancy)	Laparotomy -debulking	Died of disease	8

30	Not done	Right cystectomy (Equivocal pathology) Completion surgery: TAH BSO (all specimens negative)	Mucinous	1C	No	35	Abdominal pain	Metastatic mucinous adenocarcinoma	Platinum chemotherapy	Died of disease	39

Table 2: Detailed patient demographics of 12 patients with recurrent BOT or malignant transformation

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This Schedule B must be completed by Author in its entirety. The Publisher is unable to publish the Work unless this Schedule B is completely filled out.

MANDATED FUNDING POLICY DISCLOSURE

1. Choose a funder from the drop down list. If any of the following are selected please complete Item 2.

Please select the appropriate funder

NOTE: If you are a World Health Organization Employee and are required to publish under the Creative Commons CCBY IGO license, then do not complete this form. Instead, please contact the Editorial Office for the separate WHO Employee license agreement.

2. If you have selected funding from the above list in 1., please disclose the Open Access option to which the Work will be subject. Selecting "Gold Route" will ensure that your work is published under the Creative Commons CCBY license.

☐ Gold route

☐ Green route

NOTE: If the "Gold" route has been selected, Section 3.b. of the Agreement will apply to the Work, and neither Section 3.a. nor Section 3.c. of the Agreement will apply to the Work. If the "Green" route has been selected, Section 3.c. of the Agreement will apply to the Work after an embargo, and neither Section 3.a. nor Section 3.b. of the Agreement will apply to the Work.

3. ☐ This Schedule B is inapplicable to the Work.

NOTE: If author has selected Item 3, Section 3.a. on the Agreement will apply to the Work, and neither Section 3.b. nor Section 3.c. of the Agreement will apply to the Work.

GOVERNMENT EMPLOYEES

4. ☐ This work was created in the course of an author's employment by the United States Government

If the Work or a portion of it has been created in the course of any author's employment by the United States Government, check the "Government" box at the end of this form. A work prepared by a government employee as part of his or her official duties is called a "work of the U.S. Government" and is not subject to copyright. If it is not prepared as part of the employee's official duties, it may be subject to copyright.

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NOTE: If author has selected Item 4, Section 3. on the Agreement will not apply to the Work.

SIGNATURE PAGE

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